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HTLV-I SEROCONVERSION STUDY

ANNUAL REPORT

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A data collection research center has been established on Okinawa for the purpose of studying the risk of HTLV-I transmission to active duty personnel stationed there. Research activities have included an HTLV-I Seroprevalence Survey and a Prospective Serologic Study for HTLV-I seroconversion. A cross-sectional serologic survey of HTLV-I antibody was conducted among 5,255 active study U.S. Marines on permanent tour stationed in Okinawa, Japan to search for risk factors of seropositivity. Participants were primarily young caucasion males. Of the 28 screen possitive samples, three (.06%) were confirmed positive for HTLV-I by Western Blot analysis showing bands for core and envelope →

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reactivity. All three seropositive cases have a history of prolonged sexual contact with Okinawan women and two of the three are married to infected Okinawan wives. Two gave a prior history for gonorrhea while all 3 were negative for syphillis (MHA-TP) and Hepatitis B. No other risk risk factors associated with HTLV-I seropositivity in the U.S. population are identified. A banked sample from one individual obtained 8 months after initial sexual relations with his HTLV-I seropositive Okinawan spouse showed weak reactivity to p19 and p21E only on Western Blot and gp46 on radioimmunoprecipitation. On a sample obtained 20 months after this sample at the time of the cross-sectional survey Western Blot was strongly positive for the core p24 antibody. These data suggest that female to male transmission of HTLV-I occurs in the absence of other cofactors, e.g., ulcerative genital lesions. A prospective study in which active duty Marines are screened for HTLV-I on arrival to Okinawa and serially is being conducted. To date ~2500 personnel have been accessioned into the study with 1/2000 of the baseline sera confirmed positive for HTLV-I. There have been no seroconversions in the 800 repeat sera tested. This corroborates the findings of the seroprevalence survey which suggests that HTLV-I seroconversion occurs infrequently from the local population to the active duty personnel stationed on-island. The Seroprevalence Study will be extended to American Retirees and their Okinawan spouses to further identify correlates and efficiency of heterosexual transmission of HTLV-I.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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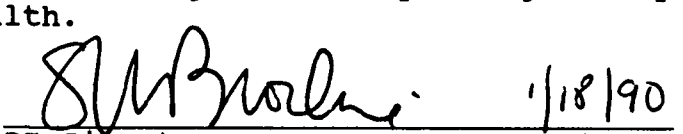

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INTRODUCTION

The second annual funding cycle of the HTLV-I Seroconversion Study has been completed. The objective of the study is to determine if Human T-cell Leukemia Virus I (HTLV-I) transmission is occurring in active duty Marines stationed on Okinawa, Japan. During the first year of the project a research unit was established on Okinawa and an HTLV-I seroprevalence survey in active duty Marines stationed on island was completed. In addition, a prospective seroconversion study in which Marines are screened for HTLV-I infection on arrival to Okinawa and then serially was initiated. (Please refer to Annual Report, 1989 for details.)

During the second year of the project, research activities have included: 1) completion of the laboratory and epidemiologic analysis of the seroprevalence survey; 2) establishment of a large cohort of participants in the prospective study; 3) implementation of on-island laboratory capability for performance of HTLV-I screening ELISA's; 4) submission of an amendment to the current proposal to expand the seroprevalence survey to the American Retirees residing on Okinawa and their Okinawan spouses; 5) poster presentation at the Vth International AIDS meeting; and 6) manuscript of the seroprevalence survey results submitted for publication. This report details the work accomplished with Year 2 funding.

Annual Report 1988-1989

Staff

The prior Annual Report detailed collaborators, contractors, and hired staff. Since that report, the following changes have occurred: 1) CDR R. Thomas was transferred from NEPMU-6 Pearl Harbor, HI to NEHC in Portsmouth. LCDR Kevin Hanson, a flight surgeon who recently completed the WRAIR Preventive Medicine Residency, is now assigned to NEPMU-6 and will be replacing CDR Thomas as an active investigator; 2) LCDR Bruce Lavin, a 2nd year fellow in Infectious Disease at NHSD, is a coinvestigator on the Retiree Study; 3) Ms. Jane Auker, R.N. has replaced Cheryl Baker as Research Nurse on Okinawa; 4) Richard Garfein, M.P.H. is a parttime Research Assistant for project activities at NHSD; 5) a new position of Medical Technologist has been created on Okinawa for the purpose of performing on-site HTLV-I ELISA's. Micki Ruggles, M.T. was hired in October, 1989 and has successfully implemented the HTLV-I screening. LCDR A. Corwin who is now reassigned to Cairo, Egypt is no longer actively collaborating on the project.

Equipment and Furniture

In addition to the equipment and space listed in the prior report, one FAX machine for Okinawa and one FAX machine for the Naval Hospital in San Diego have been purchased. This has greatly improved communication between the study site and the stateside investigators.

Space

Laboratory support is provided primarily by Biotech Laboratories as detailed in the prior report. More recently, LTCOL Roberts, Head WRWAIR Retrovirology Diagnostics Laboratory, has been providing additional laboratory collaborative support. All indeterminate and positive samples are tested by a "panel" of assays including whole virus ELISA, Cambridge Recombinant Envelope ELISA, Radioimmune Precipitation Assay, whole virus Western Blot, and p21E Western Blot to Recombinant envelope. Polymerization Chain Reaction (PCR) to differentiate HTLV-I from HTLV-II is being performed on all confirmed seropositives in Dr. Roberts' laboratory and Dr. George Shaw's laboratory, Birmingham, Alabama.

Research Activities

The Research Activities of the second year of the HTLV-I Study are as follows:

(I) Seroprevalence Survey

(II) Prospective Study

(III) Retiree Study

I. SEROPREVALENCE SURVEY

Background: The project was initiated with a cross-sectional seroprevalence survey in active duty Marines stationed on Okinawa. This was done to more rapidly approximate the risk and extent of HTLV-I infection in active duty personnel on Okinawa and to guide further studies.

II. PROSPECTIVE STUDY

The objectives and design of the HTLV-I seroconversion study are reviewed in the prior annual report. Accessioning of the prospective cohort will be completed by February, 1990 with a target study population of 3,000 planned. Follow-up of the population with annual serologies will continue. The interim results are as follows:

Prospective Participants Accessioned: ~ 2500

Questionnaires Coded and Entered: ~ 1500

Baseline Serologic Results: 1/2000 confirmed seropositive

Repeat Serologies: 0/800 seroconversions

The one confirmed case of HTLV-I infection in the baseline draw is a 21 year old Black Jamaican male. Jamaica is an endemic region for HTLV-I infection with ~ 5% of the general population being infected. He has no other identifiable risk factors for HTLV-I seropositivity. There have been no seroconversions to date in the 800 repeat draws representing 800 persons/years. This corroborates the findings of the seroprevalence survey. A follow-up questionnaire designed to better define risk behaviors

of the cohort and degree of sexual contact with Okinawans is being administered to all members of the prospective cohort.

III. RETIREE STUDY

The results of the seroprevalence survey suggests that female to male heterosexual transmission is an uncommon event in the population studied requiring prolonged sexual contact. Further information regarding the efficiency of heterosexual transmission would be useful as it could provide a basis for recommendations for prevention. In addition, further knowledge of heterosexual transmission could assist with the counselling procedures for HTLV-I infected persons which is now being done in conjunction with the mandatory screening of all blood donors.

There is a large population of U.S. military retirees residing on-island - most of whom are married to Okinawan women. Although there is no precise information as to the size of the population, it is estimated to be approximately 2,000-3,000. The seropositivity rates of HTLV-I increase with age in endemic populations so that the seropositive rates in Okinawan women over the age of 50 are 25-30%. As the retiree husbands are from a nonendemic area, this eliminates the possibility for vertical transmission of HTLV-I, a factor which has confounded other family studies done in endemic areas. Thus the retiree population on Okinawa provides a unique opportunity for study of female to male transmission of HTLV-I. The objectives of this study will be to study the efficiency and correlates of female-to-male heterosexual transmission. In addition, the clinical

consequences of adult acquired HTLV-I infection can be studied if a significant number of the husbands are infected. The likelihood of finding clinical disease is enhanced by the advanced age of the population and the probability of prolonged duration of infection.

Year Three Activities

Prospective Study

During year 3 the accessioning process will be completed and the follow-up serologies of the prospective cohort will be continued. Confirmed seroconvertors will have a full physical, laboratory screening tests, and will be counseled. Family members of all confirmed seropositives will be offered testing as well. Analysis of this population should allow for a definitive approximation of the risk in active duty Marine Corps for acquiring HTLV-I infections while on Okinawa.

Retiree Couple Study

During year 3, the demographics and extent of the retiree population on Okinawa will be defined. The study population will be retiree/Okinawan couples. Both the retiree and the spouse will be accessioned for HTLV-I serologies and epidemiologic information. Accessibility to the population can be facilitated via the retiree organizations on-island - of which there are at least 6 (e.g., Veterans of Foreign War, American Legion, Retired Enlisted Association, Retired Officer's Association, etc.). In addition, the American Consulate maintains a registration listing of retirees and mails checks to a significant proportion of the population each month. The American Consulate staff has agreed to assist with access to the population. The project will be initiated in February. VEP investigators are scheduled to address two of the on-island organizations in February 1990 and the Consulate staff has sent informational flyers out to 200 of the retirees.

Viral Epidemiology Project

Counseling Document for Individuals with HTLV-I Antibodies

Section 1 - Questions & Answers About the HTLV-I Antibody Test

What is HTLV-I?

HTLV-I is the name of a virus which was discovered approximately 10 years ago. HTLV-I stands for Human T Cell Lymphotropic Virus Type I. When this virus enters a person's body, it takes up residence in a particular type of blood cell called the T-cell. Once inside the T-Cell, the virus goes into a dormant stage and in most instances remains dormant throughout the individual's life. The virus does not go away, however, and a person infected with HTLV-I remains infected for life.

Does HTLV-I ever make people sick?

Most people that are infected with HTLV-I will not experience any illness caused by the virus. However, in rare instances HTLV-I can cause disease.

Adult T-Cell Leukemia (ALT) is a rare type of blood disease caused by HTLV-I. The people who develop this leukemia seem to have been infected with HTLV-I for many years. Current research suggests that the risk of an HTLV-I infected person developing ATL is about 1/1000 per year of infection. Many experts believe that HTLV-I infection must be acquired in infancy or childhood to result in ATL. At present there is no cure for ATL. Another disease caused by HTLV-I is called HTLV-I Associated Myelopathy (HAM). This is a progressive disease of the spinal cord. The symptoms are similar to those of Multiple Sclerosis with weakening of muscular control especially in the legs. There is

no data available regarding how frequently HAM occurs, but it is thought to be uncommon.

It is possible that there are other health problems that result from infection with HTLV-I which scientists are not aware of yet.

What does a positive HTLV-I test result mean?

A positive test for HTLV-I does not mean that you will develop either ATL or HAM, it simply means that you are probably infected with HTLV-I. There are no tests currently available which would allow us to predict which persons infected with HTLV-I will become ill. Neither are there tests available which can tell us how long a person has been infected. It is important that you understand that this is not a test for AIDS. Your blood sample was tested for the AIDS virus and was found to be negative. AIDS is caused by another virus called HIV. HIV and HTLV-I are not the same virus.

Is it possible that my test result is a mistake?

Extensive precautions have been taken to minimize the possibility of a false positive result. Every blood specimen was tested at least three times and any blood specimen which was found to be positive by one of those three tests was retested using two additional testing methods. Your blood was found to be positive for HTLV-I by all three tests. However, even with these precautions it is possible that a person may have had a false positive result. For this reason, it is advisable that all

persons having a positive test for HTLV-I have another test done on a fresh sample of blood.

One complication in testing for HTLV-I is that HTLV-I is structurally very similar to another virus called HTLV-II. It is possible that some people who test positive for HTLV-I antibodies are really infected with HTLV-II. These two viruses can be distinguished by studying the infected viral fragments in cells. This can also be accomplished with a blood sample, and this will also be done on your blood.

What is HTLV-II?

Very little is known about HTLV-II. HTLV-II is in the same family of viruses as HTLV-I and therefore probably has some of the same characteristics, such as the way it is transmitted and the duration of the infection. HTLV-II has not been shown to cause any disease, although it is possible that future research will show that HTLV-II infection has some health implications.

What should I do about this?

Most importantly you should try to keep this information in perspective. Although HTLV-I can cause serious disease, the fact is that it seldom does, especially if one acquires it as an adult. Most people infected with this virus do not experience any symptoms from this infection, indeed most live out their lives without ever knowing the virus is present.

If you are currently experiencing symptoms such as weakness or stiffness in one or both legs, numbness or heaviness in the legs, burning sensations in the feet, loss of hearing, frequency or urgency of urination, incontinence, or impotence in men, then

you should definately seek medical advice, preferably the advice of a specialist in neurology. These symptoms could be early signs of HTLV-I Associated Mylopathy (HAM). Treatment that may halt or slow the progress of HAM is available.

Beyond this it is important that you understand how HTLV-I is spread or transmitted from one infected person to another and how it is not transmitted.

How is HTLV-I transmitted?

HTLV-I is transmitted only through direct contact with body fluids such as semen, blood, and breast milk. Therefore a person with HTLV-I infection should not donate blood. In addition, such a person should not donate tissues, organs, or sperm.

One way for HTLV-I to be transmitted is by sex. More penetrative types of sexual activity (such as vaginal or anal intercourse) are more likely to pass the virus from one person to another than less penetrative activity (such as oral sex or kissing). In addition, it appears that infected men pass HTLV-I to women more readily than infected women pass HTLV-I to men. A properly used condom worn during sex should reduce the possibility of passing the HTLV-I virus to a sex partner.

Aside from sexual activity, HTLV-I may be passed from one person to another by direct blood to blood contact. Intravenous (IV) drug users who share needles also share small amounts of blood.

Another possible route of blood to blood contact between individuals is by sharing toothbrushes or razors. People with HTLV-I infection should not share these items.

At present, it is unclear whether HTLV-I can be passed directly from a mother to an unborn child in the uterus. It is possible, though not proven, that HTLV-I transmission may occur during the process of birth. What is clear, however, is that infection can be transmitted from an infected mother to a baby through breast milk. If you decide to have a child, it makes sense not to breast feed as bottle feeding carries no risk of HTLV-I transmission.

It is also important that you be aware of how HTLV-I is not transmitted. Casual contact such as talking, shaking hands, kissing on the cheeks, and hugging will not pass the virus from one person to another. Neither is HTLV-I spread by the use of bathroom facilities such as toilets, sinks, or bathtubs. The virus is not transmitted by sneezing or coughing or spitting. HTLV-I is not spread by normal daily contact at work, in school, or at home.

Section II - Additional Comments for Persons Testing Positive.

There are a couple of additional points regarding technicalities of the HTLV-I test that you may wish to know. The test which we have performed on your blood sample is an HTLV-I ANTIBODY test. Antibodies are substances which are produced by your immune system to combat infection. In some instances, such as an infection with the influenza (flu) virus, the presence of antibodies in the blood indicates that exposure occurred in the past and that the person is no longer infected. In other instances, the preserve of antibodies may indicate that the person is still infected with the virus. This is the case with

HTLV-I. When a person is infected with HTLV-I, the person develops antibodies after sufficient time elapses. The antibodies are intended to destory or eliminate the HTLV-I virus, but for some reason they are not able to accomplish this. Instead, both the HTLV-I virus and the specific antibodies remain in the blood, probably indefinitely. Since we are not yet able to routinely test blood to see if the HTLV-I virus itself is present, we must rely on the presence of the HTLV-I antibody to detect HTLV-I infection. Direct tests of the HTLV-I virus are still experimental.

It is understood that most persons who learn of their infection with HTLV-I will require some time to adjust to the information. Please feel free to telephone the Viral Epidemiology Staff to discuss any questions or concerns that you may have. People infected with HTLV-I can maximize their chances of remaining in good health by exercising reguarly, eating a well balanced diet, minimizing stress and getting adequate sleep. Tobacco, alcohol, and recreational drugs can reduce the body's capacity to resist illness and should be eliminated or at the very least, reduced.

Scientists are working to learn more about HTLV-I, the body's response to it, and the ways in which it is transmitted. The information presented here is the best presently available. It is possible that the statements and suggestions contained in this brochure will need to be changed as new information becomes available.

* Adopted from Transfusion Safety Study Counseling Document, 1989